Attorney Docket No. Enz-53(C)

REMARKS

Claims 246-252, 255, 257-260, and 264-270 are pending in the above-referenced application. As will be discussed in further detail below, claims 246 and 266 have been amended to more distinctly claim that which Applicants regard as the invention; claim 259 has been amended to correct dependency. These claim amendments are supported by the specification. No new matter has been added.

1. Rejection of Claim 268 Under 35 USC 112, First Paragraph

Claim 268 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record set forth in the office action mailed on 9/23/2005. The Office Action specifically asserts:

> Applicant asserts that there is support in the specification by way of illustration of examples in Figures 1-3 and Examples 1-4. However, the mere presence of figures that depict the presence of ligands in several positions does not offer specific support for "two or more", as instantly recited.
>
> There does not appear to be specific support for a recitation of "two or more locations" within the context of the claimed invention. Should applicants disagree, applicants are invited to point out with specificity by page and line number where any such support may exist.

Applicants respectfully traverse the rejection. In response, Applicants notes that Figure 1 depicts a primer with 8 lactyl ("L") ligands. Figure 2a depicts a primer with 2 nuclear localization ("X") moieties and 2 fusogenic peptide ("Y") moieties and Figure 2b shows the addition of 11 lactyl moleties. Figure 3 shows 4 lactyl moieties and 4 allylamine moieties that are later used for addition of fusogenic peptides. In addition there are other Figures that show the addition of Ligands to a construct. Figure 6 shows the presence of 6 Trilactyl groups. Both Figures 7 and 11 shows a nucleic acid construct with two ligands ("X") derived from extension of a primer that had two ligands. Since these Figures show the presence of 8, 11, 4, 6, 2 and 2 ligands respectively,

Applicants believe that "two or more" has been specifically illustrated in the teachings of the disclosure.

Applicants take issue with the assertion in the Office Action that there must be a specific recitation of "2 or more ligands" in the text of the specification itself. It is accepted practice that drawings may be used to fulfill the written description requirement. This has been addressed in the MPEP 2163II.A.3.(a) where it is stated:

> Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention.....
>
> An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., *Vas-Cath*, 935 F.2d at 1565, 19 USPQ2d at 1118 ("drawings alone may prove a 'written description' of an invention as required by Sec. 112*"); *In re Wolfensperger*, 302 F.2d 950, 133 USPQ 537 (CCPA 1962) (the drawings of applicant's specification provided sufficient written descriptive support for the claim limitation at issue); *Autogiro Co. of America v. United States,* 384 F.2d 391, 398, 155 USPQ 697, 703 (Ct. Cal. 1967) ("In those instances where a visual representation can flesh out words, drawings may be used in the same manner and with the same limitations as the specification.").

In the instant situation, there are clearly several representations of "2 or more ligands" in the figures. Thus, no new matter has been added.

In view of the above arguments, Applicants assert that the rejection of claim 268 under 35 USC 112 (new matter) has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

2.The Objection to Claim 266

Claim 266 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. In response, claim 266 has been amended to recite that the construct is neutral.

In view of the amendment of claim 266, the objection to this claim has been overcome. Thus, Applicants respectfully request that the objection be withdrawn.

3. The Rejection of Claims 259 and 260 Under 35 USC 112, Second Paragraph

Claims 259 and 260 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action specifically states:

> Claim 259 recites the limitation "The construct of claim 246, wherein said synthetic polymer.. ." However, claim 246 does not recite a synthetic polymer. There is insufficient antecedent basis for this limitation in the claim. Claim 260 is rejected because it depends from claim 259.

In response, Applicants note that claim 259 has been amended to recite to depend from claim 257, which recites a synthetic polymer. Given the amendment of claim 259, the rejection of claim 260 is overcome as well.

In view of the amendment of claim 259, the rejection of claims 259 and 260 under 35 USC 112, second paragraph has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

4. The Rejection of Claims 246-252, 255, 257, 258 and 264-270 Under 35 USC 112, First Paragraph (Written Description/New Matter)

Claims 246-252, 255, 257, 258 and 264-270 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. It is further asserted that this is a new matter rejection. The Office Action specifically states:

> The instant claims are directed to a chemically modified nucleic acid construct, said construct comprising a modified nucleotide, a nucleotide analog, or a combination of the foregoing, wherein said modified nucleotide or nucleotide analog comprises a non-nucleic acid entity, "wherein said non-nucleic acid entity confers nuclease resistance, cell targeting, cellular localization or nuclear localization, or a combination of the foregoing".

> The specification discloses that "non-nucleic acid entity or entities" include natural polymers, synthetic polymers, natural ligands and synthetic ligands, as well as combinations of any and all of the foregoing. When' the non-nucleic acid entity or entities take the form of a natural polymer, suitable members may be modified or unmodified. Natural polymers can be selected from a polypeptide, a protein, a polysaccharide, a fatty acid, and a fatty acid ester as well as any and all combinations of the foregoing.
>
> The amendment to claim 246 to recite "wherein said non-nucleic acid entity confers nuclease resistance, cell targeting, cellular localization or nuclear localization, or a combination of the foregoing" is new matter because the specification only teaches that chemical modifications or ligands can confer nuclease resistance, cell targeting, cellular localization or nuclear localization and does not teach that any "non-nucleic acid entity" or entities confer such results.

Applicants respectfully traverse the rejection. It is Applicants view that examples of a number of non-nucleic acid entities besides ligands conferring properties are explicitly shown in various places in the specification. It should be pointed out that the specification states that the chemical modification is a means that allows attachment of non-nucleic acid moieties that can be responsible for conferring one or more of the properties described above. Thus, a nucleotide can be used that contains a chemically reactive moiety such as allylamine where any desirable entity can be attached to the nucleotide to provide a useful property. For example, page 34 of the specification states:

> The present invention uses chemical modification of nucleic acid to **attach** directly or indirectly one or more ligands or chemical modifications **or other moieties** to a nucleic acid construct.

Additionally, the list of various non-nucleic acid entities that is presented on page 36 (and quoted on page 5 of the Office Action) is substances that can be joined to a construct through a chemically modified nucleotide or nucleic acid. The inclusion of other moieties besides ligands and the chemical modification itself is disclosed in numerous locations within the specification. Two examples of such recitations are on page 39 of the specification:

> Modifications of sugar and phosphate moieties can be preferred sites for terminal binding of ligands or chemical modifications **and other moieties**
>
> Modifications of the base moieties can be utilized for both internal and or terminal binding of ligands or chemical modifications **and other moieties**.

Pages 41-44 also provide several examples of non-nucleic acid moieties.

Further examples are provided in the figures. For example, Figure 2 show a nucleic acid that has been chemically modified such that it now comprises moiety "X" that confers a nuclear localization signal and moiety "Y" that is a fusogenic peptide. For example, Figure 3 (and described as Example 4) shows incorporation of two varieties of nucleotides, lactyl-UTP that contains a ligand and allyllamine-UTP that is a chemically modified nucleotide. A useful property is then conferred upon the construct by the addition of a fusogenic property to the allyl amine chemical group; i.e. The chemical modification allowed attachment of a non-nucleic acid entity that can contribute to entry of the construct into the cell.

Applicants note that this rejection should only be applicable to claims 246-252, 255, 257-260, 264-267. Claim 268 does not have any recitation of a "non-nucleic acid entity"; claims 269-270 depend from claim 268.

In view of the above arguments, Applicants assert that the rejection under 35 USC 112, written description, has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn. Furthermore, Applicants assert that the instant claims be accorded the priority date of the instant application December 1995..

5. The Rejections Under 35 USC 102

Two prior art rejections were made. They are discussed below.

5.1 Pardridge et al.

Claims 246-252, 255, 257, 258, and 264-267 are rejected under 35 U.S.C. 102(a) as being anticipated by Pardridge et al. (Proc. Natl. Acad. Sci. , Pharmacology, June 1995, Vol. 92, pages 5592-5596). The Office Action specifically states

> Pardridge et al. teach that PNAs are nucleic acid molecules with antisense effects that may prove to be effective pharmaceuticals if they can undergo transport through the brain capillary endothelial wall. Pardridge et al. teach that PNAs have a neutral backbone and that it is necessary to use delivery systems for these molecules, such as vector mediated peptide-drug delivery systems. Pardridge et al. teach an 18- mer that is antisense to the *rev* gene and is biotinylated and linked to a conjugate of . streptavidin (SA) and the **OX26** murine monoclonal antibody. The PNA nucleic acid construct of Pardridge et al. comprises a nucleotide analog and a non-nucleic acid entity. Pardridge et al. teach that the PNAs are analogues of DNA in which the backbone is modified and replaced with a polyamide backbone. The PNA nucleic acid constructs "directs the synthesis" of a nucleic product having biological activity because the PNA is able to bind to *rev* mRNA. Therefore, since the PNA is able to inhibit the synthesis of a nucleic product, the PNA "directs the synthesis", as instantly claimed.
>
> The PNA of Partridge et al. is linear and single-stranded. The single-stranded PNA is considered to comprise a polynucleotide tail that is hybridized to a complementary polynucleotide sequence. The PNA is modified via attachment to biotin. The non-nucleic acid entity is the peptide nucleic acid backbone wherein the phosphate backbone is replaced with a polyamide backbone (see Materials and Methods) and are synthetic polymers, more specifically heteropolymers.
>
> The instant specification teaches that "Nucleic acid analogues are polymers capable of binding to a complementary nucleic acid and in which these polymer backbones are other than ribo- and deoxyribose sugars and phosphate groups or in which side chain groups are other than natural or modified bases. Examples of nucleic acid analogue polymers include peptide nucleic acids.. ."(see page 37, last paragraph). Therefore, the chemically modified nucleic acid construct of Pardridge et al. anticipates the instant claims.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claim 246 has been amended to recite that the construct when present in a cell is used as a template for the synthesis of a nucleic acid product having biological activity. This claim amendment is supported by the specification in Example 7. This

example actually describes the construction of an RNA derived CHENAC. The second sentence of Example 7 states

> Transcription is carried out in vitro by use of a T7 promoter directing the synthesis of the sequences of interest.

Furthermore, a drawing of the construct described in Example 7 is shown in Figure 7.

Further support is found in Example 8 and correspondingly Figure 9 where it is stated

> A construct is made with the appropriate structure shown in Figure 9. Transcription is carried out in vitro by use of a T7 promoter directing the synthesis of the sequences of interest.

Applicants assert that claim 246 can be distinguished from Pardridge. Pardridge et al., essentially describes an oligo antisense reagent that is made of analogues of normal nucleotides. The peptide nucleic acids are distinguished by using an uncharged backbone instead of the normal phosphate connections. Contrary to the assertions in the Office Action, these compounds would not be considered to "direct" the synthesis of nucleic acids even in the loose way being used here. Antisense is believed to involve either degradation of mRNA or to block the ability of mRNA to be used for translation into a protein, and as such the point of action of antisense is not considered to be on the level of transcription. As such, there is no indication in Pardridge that the rate or level of synthesis of rev mRNA is affected by the presence of their PNA conjugate. Furthermore, one skilled in the art would understand that "directs the synthesis" is an indication that the construct provides the template for nucleic acid synthesis and is not meant to indicate an influence on synthesis from native genes of the target cell. Thus, claim 246 is not anticipated by Pardridge et al.

Claims 247-252, 255, 257-260 and 264-267 ultimately depend from claim 246. Therefore arguments made with respect to claim 246 would be applicable to these claims as well.

In view of the amendment of claim 246 and the above arguments, Applicants assert that the rejections under 35 USC 102 over Pardridge et al. have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

5.2 Craig et al.

Claims 268-270 are rejected under 35 U.S.C. 102(a) as being anticipated by Craig et al. (WO95106129). The Office Action specifically states

> Craig et al. teach a complex comprising a biologically active agent, such as a nucleic acid that comprises a transcription unit encoding a RNA molecule that is capable of eliciting a biological effect, and ligands that are capable of binding to a target cell (see page 5 and 7). Craig et al. teach that the product of the transcription unit may be an RNA molecule, such as an antisense RNA molecule or a ribozyme and the ligand is any entity capable of binding to the surface of a cell, such as proteins or nucleic acids (see page 8). The ligand was bound in various positions on the construct. The construct comprises a sequence that encodes an antisense oligonucleotide, wherein the sequence has a terminus that necessarily comprises a polynucleotide tail, wherein the polynucleotide tail sequence can hybridize to a complementary sequence.
>
> Therefore, the instant claims are anticipated by Craig et al.

Applicants respectfully traverse the rejection. Craig et al. essentially describes the use of a ligand that is complexed to DNA. The Examples in Craig et al. give a teaching of using polylysine which binds to nucleic acids through charge interactions but does not participate in any sort of chemical reaction or modification of the nucleic acids (see page 17 and section entitled "Preparation of antibody-polylysine:DNA complexes"). There is never any indication of a covalent attachment of the nucleic acid to any member of the complexes described by Craig et al. This is witnessed by the fact that there is no suggestion or teaching for chemical modification of a nucleotide or nucleotides which would allow **covalent** attachment of the nucleic acid to other moieties. The use of polylysine would be a situation where a nucleic acid is bound non-covalently and this would be irrespective if there were any covalent bonds joining the polylysine to some other entity.

Claims 269-270 depend from claim 268. Therefore, arguments made with respect to claim 268 are applicable to claims 269-270 as well.

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In view of the above arguments, Applicants assert that the rejection of claim 268-270 under 35 USC 102 has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

6. Summary and Conclusions

Claims 246-253, 255-262 and 264-270 are pending in the above-referenced application. Claims 253, 256 and 261-262 have been canceled without prejudice. Claims 246, 249, 259 and 266 have been amended to more distinctly claim that which Applicants regard as their invention.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at (914) 712-0093.

Respectfully submitted,

10/15/07

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